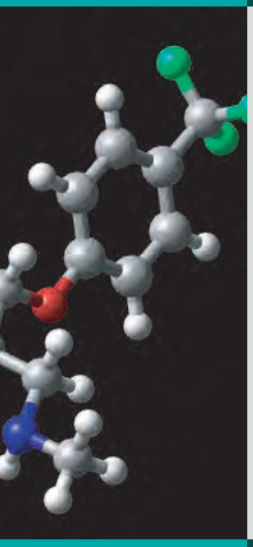

QikProp

Rapid ADME predictions of drug candidates

QikProp efficiently evaluates a widely applicable set of pharmaceutically relevant properties at a rate of over a quarter of a million compounds per hour, making it an indispensable tool for applying ADME principles in lead discovery and optimization.

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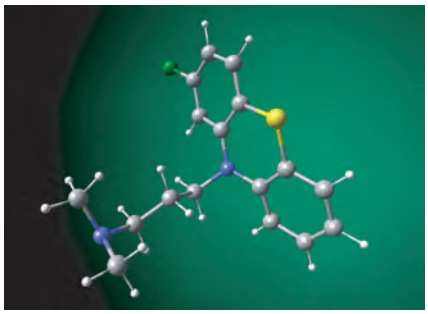
The Advantages of ADME Properties Prediction

Nearly 40% of drug candidates fail in clinical trials due to poor ADME (absorption, distribution, metabolism, and excretion) properties. These late-stage failures contribute significantly to the skyrocketing cost of new drug development. The ability to detect problematic candidates early will dramatically reduce the amount of wasted time and resources, and streamline the overall development process.

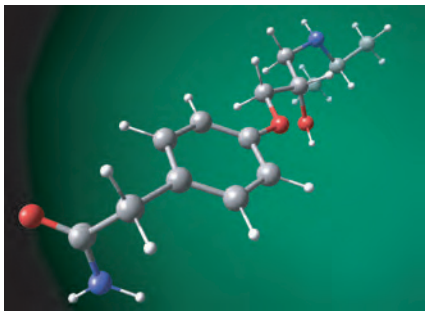
Accurate ADME properties prediction prior to expensive experimental procedures, such as HTS, can eliminate unnecessary testing on compounds that are doomed to fail; it can also focus lead optimization efforts to enhance the desired ADME properties. Finally, incorporating ADME predictions as a part of the development process will result in lead compounds that are more likely to exhibit satisfactory ADME performances during clinical trials

QikProp computed properties compared against experiment for several well-known drugs:

Molecule	QP log P (o/w)	Expt log P (o/w)	QP log S	Expt log S	QP log BB	Expt log BB
atropine	2.62	1.83	-2.08	-2.12	0.09	n/a
diflucan (fluconazole)	1.98	0.50	-2.71	-1.80	-0.60	n/a
ibuprofen	3.35	3.50	-3.45	-3.76	-0.48	-0.18
indomethacin	3.74	4.27	-4.79	-4.62	-0.68	-1.26
lorazepam	2.48	2.51	-4.41	-3.60	-0.40	n/a
progesterone	3.64	3.87	-4.59	-4.42	-0.24	n/a
triflupromazine	5.36	5.19	-5.29	-5.30	1.01	n/a



Antipsychotic drug chlorpromazine is shown above. This drug is extremely hydrophobic and thus has relatively poor solubility (high log P), and high serum-protein binding, but good cell permeability.



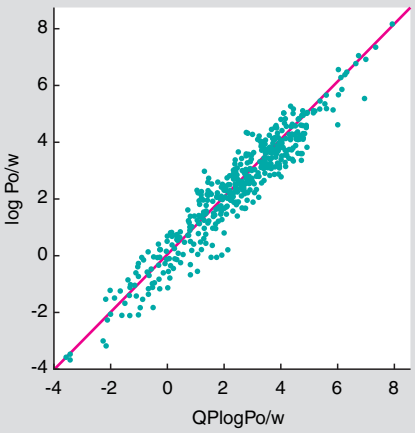
Adrenergic atenolol is shown above. This compound is extremely hydrophilic and thus has relatively good solubility (low log P), and low serum-protein binding, but poor cell permeability.

QikProp: Maximizing Returns in Drug Discovery

Schrödinger's QikProp is an extremely fast ADME properties prediction program. It provides the following benefits:

- **Wide range of predicted properties:** QikProp predicts the widest variety of pharmaceutically relevant properties - octanol/water and water/gas log Ps, log S, log BB, overall CNS activity, Caco-2 and MDCK cell permeabilities, human oral absorption, log K_{hsa} for human serum albumin binding, and log IC_{50} for HERG K^+-channel blockage – so that decisions about a molecule's suitability can be made based on a thorough analysis.
- **Accurate ADME properties:** QikProp bases its predictions on the full 3D molecular structure; unlike fragment-based approaches, QikProp can provide equally accurate results in predicting properties for molecules with novel scaffolds as for analogs of well-known drugs.
- **Lipinski Rule-of-Five and Jorgensen Rule-of-Three:** QikProp has the ability to check for Lipinski Rule-of-Five and Jorgensen Rule-of-Three violations to provide an at-a-glance measure of whether a compound is drug-like.
- **Similarity:** QikProp automatically identifies compounds most similar to processed ligands from a 1700 molecule database of orally available drugs, or from a user-specified library of molecules.
- **Lead generation:** QikProp rapidly screens compound libraries for hits. QikProp identifies molecules with computed properties that fall outside the normal range of known drugs, making it simple to filter out candidates with unsuitable ADME properties.
- **Lead optimization:** QikProp can play an important role during lead optimization by analyzing similarity within a class of compounds as well as by identifying compounds to avoid because they exhibit extreme values of predicted properties.
- **Improving accuracy:** QikProp computes over twenty physical descriptors, which can be used to improve predictions by fitting to additional or proprietary experimental data, and to generate alternate QSAR models.
- **Easy-to-use interface:** QikProp accepts a wide variety of input formats, including Maestro files, MDL SD files, and PDB files; calculations are easily set up, and results can be plotted and analyzed using the Maestro user interface.

Performance-Driven Technology



QikProp-predicted water/octanol partition coefficients are plotted against experiment. Excellent agreement (r^2 = 0.92, and RMSD = 0.54) is seen for this predicted property across over four hundred pharmaceutically relevant compounds. Similar agreement is seen for all QikProp-predicted properties.

QikProp attains its success through superior technology:

- **Trained on well-known drugs:** Developed in Professor Bill Jorgensen's laboratory at Yale University, QikProp is parametrized against about 500 drugs and related heterocycles to ensure the accuracy of its predictions.
- **Physically meaningful descriptors:** QikProp uses descriptors that are derived from molecular structure and computed molecular properties. QikProp also recognizes about 30 types of reactive functional groups, which could lead to false positives in HTS assays; and suggests likely metabolic processes.
- **High performance:** QikProp provides two modes of calculation. In fast mode, QikProp can process over a quarter of a million compounds per hour.
- **QikSim:** An included QikProp module that compares every molecule to a target compound with simple Euclidian and Tanimoto measures of similarity.
- **QikFit:** An included QikProp module that generates linear regression equations to describe the relationship between a new, user-specified experimental property and QikProp descriptors and properties.

ADME Properties and Bioavailability

QikProp-predicted and experimental (in parentheses) ADME properties

	Chlorpromazine	Atenolol
log S	-4.74 (-5.01)	-0.49 (-1.30)
log P	4.91 (5.19)	0.20 (0.16)
log BB	0.92 (1.06)	-1.20
log K_{hsa}	0.75 (1.10)	-0.76 (-0.48)
PCaco (nm/s)	2124	35 (33)
PMDCK (nm/s)	4839	33 (18)
CNS Activity	++	--

QikProp predicted properties for the antipsychotic drug chlorpromazine (Thorazine) and the antiadrenergic atenolol are listed in the table. The two drugs approach the hydrophobic and hydrophilic extremes, respectively, and illustrate a typical pattern - hydrophobic compounds have relatively poor solubility, high log P, and high serum protein binding, but good cell permeability; whereas the opposite is true for hydrophilic compounds. This dichotomy is responsible for the classic lead-optimization struggle of solubility versus permeability. QikProp can be extremely useful in this process by making predictions for a proposed series of analogs, and identifying potential problems early. An example of a promising compound that eventually failed is a peptide like thrombin inhibitor, which had to be abandoned late in development due to its poor oral bioavailability of only 1%. QikProp easily reveals the problem as poor cell permeability for this relatively polar molecule, with predicted PCaco and PMDCK values near 10 nm/s.

Evaluation Copies

To request an evaluation copy of QikProp, please contact info@schrodinger.com. Our staff of support scientists will be happy to assist you in giving QikProp a thorough trial.

QikProp

Rapid ADME predictions of drug candidates

A Coordinated Family of Products

QikProp generates accurate ADME properties, which can be used to rapidly screen ligand libraries for hits to pass to the next phase of virtual screening using ligand-receptor docking by **Glide**. In addition to Glide, Schrödinger's structure based analyses contain three more integrated modules:

- **Liaison:** Ligand-receptor binding free energies for lead optimization
- **QSite:** Mixed QM/MM for reactive chemistry at the enzyme active site
- **Strike:** Statistical modeling and QSAR for developing structure-activity relationships.

Complementing the structure-based suite is **Phase**, a ligand-based drug design program that performs pharmacophore modeling.

All Schrödinger products are seamlessly integrated through the Maestro graphical interface.

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